Synthesis of 4,5-diazaspiro[2.3]hexanes and 1,2-diazaspiro[3.3]heptanes as hexahydropyridazine analogues

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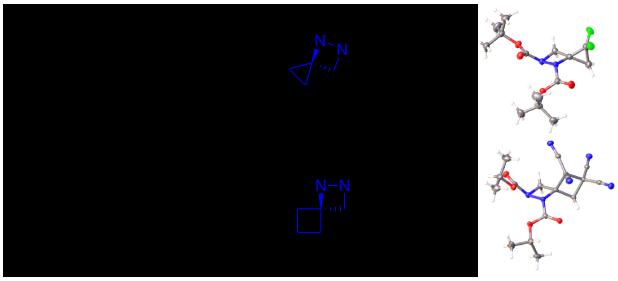
TABLE OF CONTENTS/ABSTRACT:

4,5-Diazaspiro[2.3]hexanes are made by dihalocarbene addition across the exocyclic double bond of readily accessible 3-alkylidene-1,2-diazetidines. Using difluorocarbene, generated from $TMSCF_3$/NaI, these spirocycles were produced in yields up to 97% by stereospecific addition across the alkene. Lower yields (up to 64%) were observed using more reactive dichlorocarbene, due to competitive insertion of the carbene into the N–N bond. Larger 1,2-diazaspiro[3.3]heptanes are produced by [2+2] cycloaddition of 3-alkylidene-1,2-diazetidines with tetracyanoethylene (TCNE) in up to 99% yield.

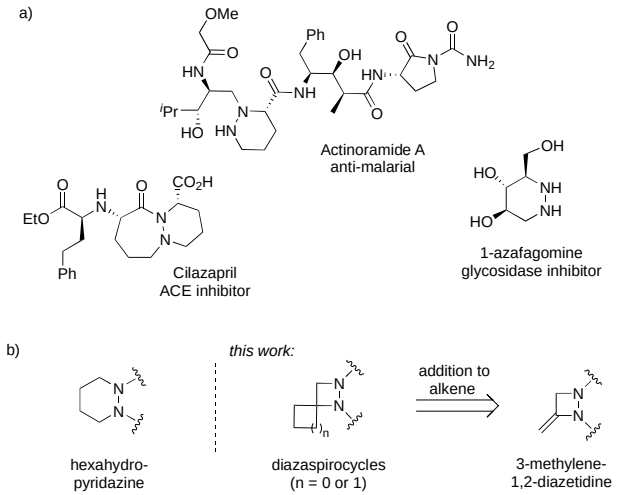


Spirocyclic heterocycles are emerging as valuable tools in medicinal chemistry,[1,2] with those containing a four-membered ring being of prominent interest.[3] In general, spirocycles have a number of properties beneficial to medicinal chemistry programs including their inherent rigidity, structural novelty, reduced lipophilicity and potential to place attached functional groups precisely in three-dimensional space. Through the development of chemistry of new heterocyclic systems, there is scope to create novel spirocyclic scaffolds that can open up uncharted regions of chemical space for drug discovery. In this

Note, we report efficient methods for the functionalization of the exocyclic double bond of 3-alkylidene-1,2-diazetidines, providing entry to 4,5-diazaspiro[2.3]hexanes and 1,2-diazaspiro[3.3]heptanes as potential hexahydropyridazine analogues**.**

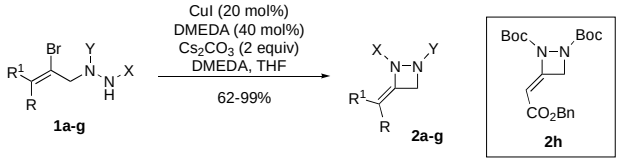
The pyridazine nucleus containing two adjacent nitrogen atoms within a six-membered ring is a privileged substructure in medicinal chemistry.[4] An important member of this group is the saturated hexahydropyridazine nucleus, with a number of molecules including actinoramide A,[5] cilazapril,[6] and 1-azafagomine[7] possessing prominent bioactivity (Figure 1a). Since introduction of a spirocenter into other saturated nitrogen heterocycles has proved valuable,[1,2] we reasoned that rigidification of the hexahydropyridazine nucleus might have considerable merit. With this in mind, we targeted the synthesis of 4,5-diazaspiro[2.3]hexanes and 1,2-diazaspiro[3.3]heptanes as analogues of the hexahydropyridazine nucleus (Figure 1b). Our planned approach to these frameworks was to exploit carbene additions (n = 0) and [2+2] cycloadditions (n = 1) of readily accessible 3-methylene-1,2-diazetidines.[8-10] At the outset of this study, very little was known about the reactivity of these unsaturated heterocycles.[8,10-12] Iacobini et al. have reported Rh-catalyzed asymmetric hydrogenations producing 3-alkyl-1,2-diazetidines in up to 89% ee.[11] Brown et al. have described Pd-catalyzed Heck reactions as a way to introduce additional substituents on the exocyclic double bond.[8] Very recently, Okitsu et al. have reported nucleophilic ring opening of 3-methylene-4-amido-1,2-diazetidines with silyl enol ethers and allyltrimethylsilanes.[10]

Figure 1. (a) Illustrative bioactive molecules containing the hexahydropyridazine nucleus. (b) Planned strategy to 4,5-diazaspiro[2.3]hexanes (n = 0) and 1,2-diazaspiro[3.3]heptanes (n = 1) and their potential use as rigidified hexahydropyridazine analogues.



A series of 3-alkylidene-1,2-diazetidines **2a-g** was made to explore this chemistry. They were conveniently made by copper catalyzed ring closure of the corresponding 2-bromo-2-propenyl hydrazines **1a-g** in the presence of N,N'-dimethylethylenediamine (DMEDA) and cesium carbonate (Scheme 1).[8] The synthesis of the requisite precursors **1a-g** was straightforward (see Experimental Section). The Cu-catalyzed ring closure is known to proceed with net stereochemical retention at the vinylic carbon.[8] Thus, (*Z*)-**2d** was produced from (*Z*)-**1d** as a single geometric isomer. Of further note, the synthesis of **2g** provides the first example of a 3-alkylidene-1,2-diazetidine bearing different groups on the two nitrogen atoms allowing selective deprotection/functionalization of the heteroatoms. Finally, **2h** bearing a benzyl ester on the double bond was produced from benzyl allenoate and di-*tert*-butyl azodicarboxylate according to the method of Xu.[9]

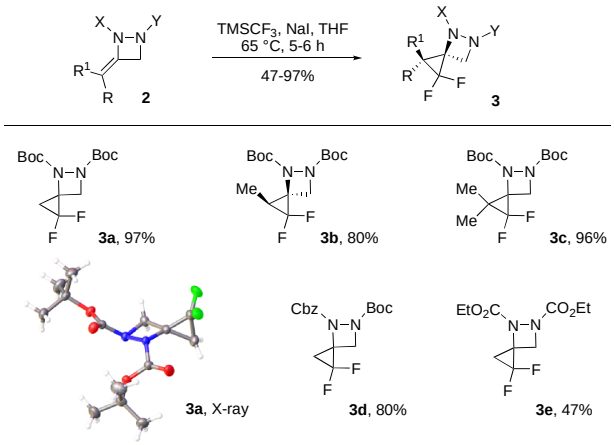
Scheme 1. Copper catalyzed ring closure to 3-alkylidene-1,2-diazetidines 2a-g.



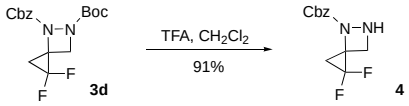
where **a**: R, R^1 = H, X, Y = CO_2Et; **b**: R, R^1 = H, X, Y = $CO_2{}^iPr$;
c: R, R^1 = H, X, Y = Boc; **d**: R = H, R^1 = Me, X, Y = Boc;
e: R, R^1 = Me, X, Y = CO_2Et; **f**: R, R^1 = Me, X, Y = Boc;
g: R, R^1 = H, X = Cbz, Y = Boc.

With **2a-h** in hand, we first explored the addition of carbenes to the exocyclic double bond of these heterocycles. Preliminary experiments indicated that dihalocarbenes possess the correct balance of reactivity/stability for this transformation.[13] Our first success came with the synthesis of 4,5-diazaspiro[2.3]hexane **3** by way of difluorocarbene[14] addition to 3-alkylidene-1,2-diazetidine **2**. Treatment of *bis*-Boc **2c** with the Ruppert-Prakash reagent $TMSCF_3$ and NaI according to the method of Wang[15] provided **3a** in essentially quantitative yield (Scheme 2). The structure of this product was unambiguously established by single-crystal X-ray diffraction. In the solid-state, the two nitrogen atoms display highly pyramidal geometries with the Boc groups projecting on opposite faces of the four membered ring (Scheme 2). The introduction of fluorine into drug structures to block sites of metabolism and improve physicochemical properties is well understood.[16] In **3a**, these fluorine atoms also appear to play a role in controlling the N-stereochemistry with the difluoromethylene and the adjacent Boc group orientating themselves away from one another in the solid-state. Further exploration of the scope of this reaction reveals that it works well for di-, tri- and tetrasubstituted alkenes, and tolerates variation in the N-substituent. In the difluorocarbene addition to (*Z*)-**2d**, only a single diastereoisomer was produced. This was assigned as **3b** on the basis of NOE experiments (see Supporting Information), consistent with stereospecific addition across **2d** with net retention of the olefin geometry (see Supporting Information). To illustrate that differentiation of the nitrogen atoms in the 1,1-difluoro-4,5-diazaspiro[2.3]hexanes is feasible, selective removal of the Boc group from **3d** was achieved using TFA providing **4** in excellent yield (Scheme 3).

Scheme 2. Synthesis of 1,1-difluoro-4,5-diazaspiro[2.3]hexanes.

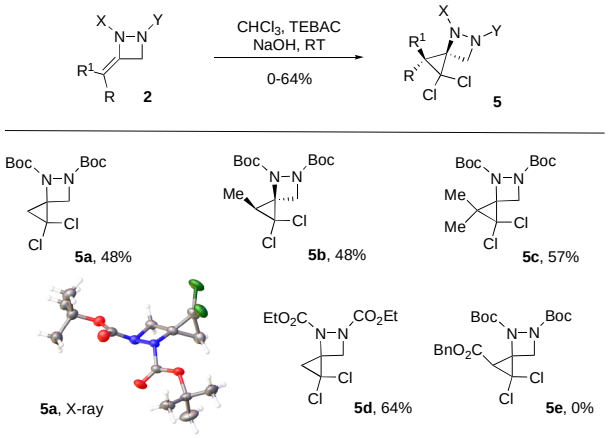


Scheme 3. Selective deprotection of 4.



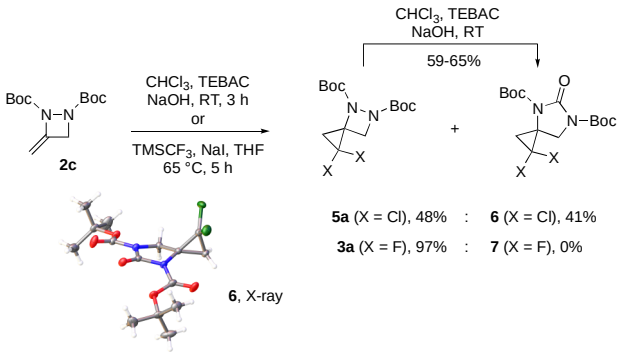
Encouraged by these findings, we examined the reaction of 3-methylene-1,2-diazetidine **2** with dichlorocarbene, formed by base induced α-elimination of chloroform. The method of Makosza et al. using triethylbenzylammonium chloride (TEBAC) as phase transfer catalysis was used.[17] Moderate to good yields of the corresponding 1,1-dichloro-4,5-diazaspiro[2.3]hexanes were realized (Scheme 4). However, with one exception (**2a**), lower yields were observed in comparison to the difluorocarbene additions (Scheme 2). For example, **5a** was produced in 48% yield compared to 97% for **3a**. In the case of **2h** bearing an electron-withdrawing group, we were unable to isolate any of the desired addition product. Optimization of the reaction time with careful monitoring of product formation by TLC was necessary to obtain satisfactory yields in these dichlorocarbene additions. For example, the yield of **5c** could be improved from 42% to 57% by reducing the reaction time from 240 to 75 min. Again, a single diastereomer of **5b** was produced through stereospecific addition. In the case of **5a**, single crystal XRD was used to confirm the spirocyclic nature of the product.

Scheme 4. Synthesis of 1,1-dichloro-4,5-diazaspiro[2.3]hexanes.



The lower yields witnessed in the dichlorocarbene additions arise from an unexpected ring expansion reaction. For example, in the reaction of **2c** with dichlorocarbene, a near equal quantity of ring expanded urea **6** was isolated alongside diazaspiro[2.3]hexane **5a** (Scheme 5). Formation of the urea C=O bond presumably arises from dichlorocarbene insertion into the N–N bond, followed by hydrolysis of the two labile C–Cl bonds under the aqueous reaction conditions. Although this process is essentially unprecedented, we note that Taylor and Davies have reported intramolecular insertion of a rhodium carbenoid into the N–N bond of a 1,2-diazetidin-3-one.[18] No products derived from carbene insertion into the N–N bond without prior addition to the exocyclic double bond were observed. Moreover, resubjection of spirocycle **5a** to the cyclopropanation conditions led to formation of **6** in 65% yield. Combined with the observation that shorter reaction times led to improved yields of the 1,2-dichloro-4,5-diazaspiro[2.3]hexanes in some instances, these experiments suggest that carbene addition across the double bond is the faster process, with further ring expansion of the diazetidine ring occurring in the presence of excess dichlorocarbene. Whilst ring expansion is not seen in reactions involving difluorocarbene (Scheme 2), indirect access to these products is possible by treatment of 1,1-difluoro-4,5-diazaspiro[2.3]hexane **3a** with *dichlorocarbene* leading to **7** in 59% yield (Scheme 5).

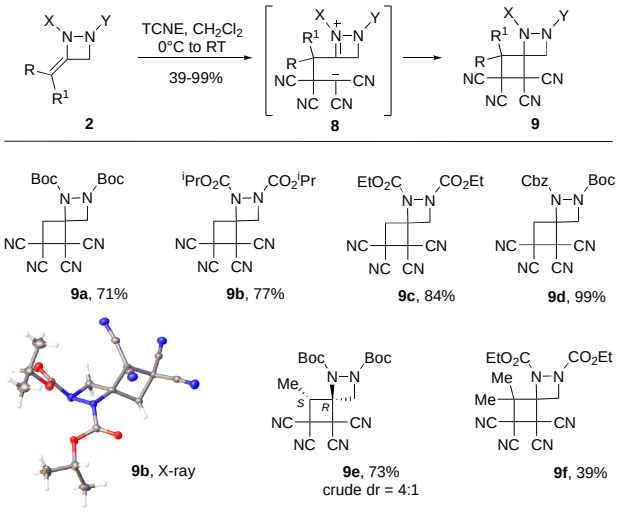
Scheme 5. Further insights into the carbene addition reactions.



As tetracyanoethylene (TCNE) is known to be an excellent partner for [2+2] cycloadditions, especially with electron-rich alkenes,[19] we next chose to examine its use for the formation of the ring expanded 4,5-diazaspiro[3.3]heptanes. Indeed, treatment of **2** with TCNE (1.0-1.5 equiv) in dichloromethane provided 4,5-diazaspiro[3.3]heptanes **9a-f** in good to excellent yields (Scheme 6). The chemical efficiency of the reaction lowers with increasing steric bulk of the carbamate groups, and with increased substitution of the double bond. The solid-state structure of the spirocycles was unambiguously established by single crystal X-ray diffraction of **9a** (Scheme 6). To our initial surprise, the major product **9e** formed in 73% yield by reaction of (*Z*)-**2d** with TCNE possesses (*R*,*S*)-stereochemistry. This relative stereochemistry was confirmed by NOE experiments, which indicated that the methyl group is located on the same face as the methylene group of the diazetidine ring (see Supporting Information). A small quantity of the (*R*,*R*)-diastereomer was also produced (crude d.r. = 4:1) but this proved unstable to column chromatography. Unlike the carbene additions to (*Z*)-**2d** which proceed stereospecifically with retention of the olefin geometry in **3b** and **5b**, (*R*,*S*)-**9e** arises from inversion of configuration with respect to the starting alkene. This outcome suggests that the reaction proceeds in a stepwise manner via zwitterionic intermediate **8**, with subsequent ring closure to (*R*,*S*)-**9e**.[20] TCNE reactions with electron-rich alkenes commonly proceed in this manner.[19] Analysis of molecular models indicates that (*R*,*S*)-**9e**

is less sterically crowded than the (*R*,*R*)-diastereomer, which presumably explains why it is favored in ring closure of **8**.

Scheme 6. Synthesis of diazaspiro[3.3]heptanes by reaction of 2 with TCNE.



In conclusion, we have developed a practical and efficient synthesis of a series of 4,5-diazaspiro[2.3]hexanes and 1,2-diazaspiro[3.3]heptanes by addition reactions of 3-alkylidene-1,2-diazetidines. Halogenated 4,5-diazaspiro[2.3]hexanes are produced in good to excellent yields by concerted carbene additions to the double bond. With dichlorocarbene, a novel ring expansion of the four membered diazetidine ring by way of insertion into the N–N bond was also discovered. Using TCNE, a homologous series of 1,2-diazaspiro[3.3]heptanes was produced in good yields by highly asynchronous [2+2] cycloadditions. Work to explore the potential of these spirocycles in medicinal chemistry programs as hexahydropyridazine analogues is ongoing.

EXPERIMENTAL SECTION

The synthesis of **2a**,[8] **2c**,[8] **2f**[8] and **2h**[9] followed published methods. NMR assignments were deduced using 2D experiments (COSY, HMBC, and HMQC).

Synthesis of hydrazodicarboxylates 1b, 1d and 1e: General Procedure.

To a solution of the alcohol (1.0 molar equiv) and triphenylphosphine (2.0 molar equiv) in anhydrous THF at 0 °C was added the azodicarboxylate (2.0 molar equiv) portionwise. The mixture was allowed to warm to room temperature, stirred for the stated period then concentrated in vacuo. Purification by column chromatography provided the products as detailed below.

Di-iso-propyl 1-(2-bromoallyl)hydrazine-1,2-dicarboxylate **(1b)**

2-Bromoallyl alcohol (1.56 g, 11.4 mmol), triphenylphosphine (5.98 g, 22.8 mmol) and di-*iso*-propyl azodicarboxylate (4.49 mL, 22.8 mmol) in anhydrous THF (120 mL) were reacted according to the general procedure for 24 h. Purification by column chromatography (SiO_2, 7:1 petrol/ ethyl acetate) provided **1b** (2.75 g, 75%) as a white solid: m. p. 68–69 °C; υ_{max} (film)/cm^{-1} 3284, 2964, 1736, 1682; δ_H (400 MHz, $CDCl_3$) 6.84–6.42 (1H, br m, NH), 5.85–5.74 (1H, m, CBr=C*H*H), 5.57 (1H, s, CBr=CH*H*), 5.01–4.86 (2H, m, 2 x C*H*$(CH_3)_2$), 4.50–4.13 (2H, m, NC*H*$_2$CBr), 1.23 (12H, d, *J* = 6.2 Hz, 4 x CH_3); δ_C (100 MHz, $CDCl_3$) 155.5 (COO), 155.3 (COO), 128.2 (CH_2=*C*Br), 119.9 (*C*H_2=CBr, rotamer), 119.4 (*C*H_2=CBr, rotamer), 70.6 (CO_2*C*H$(CH_3)_2$), 70.0 (CO_2*C*H$(CH_3)_2$), 58.0 (N*C*H_2CBr, rotamer), 57.3 (N*C*H_2CBr, rotamer), 22.0 (2 x CH_3), 21.9 (2 x CH_3); MS (ESI^+) *m/z* 345 (M(^{79}Br)Na^+), 347 (M(^{81}Br)Na^+); HRMS (ESI/TOF-Q) *m/z* $[M + Na]^+$ calcd for $C_{11}H_{19}{}^{79}BrN_2O_4Na$ 345.0420; found 345.0416.

Di-tert-butyl (Z)-1-(2-bromo-2-butenyl)hydrazine-1,2-dicarboxylate **(1d)**

(*Z*)-2-Bromo-2-buten-1-ol[21] (1.92 g, 12.7 mmol), triphenylphosphine (6.66 g, 25.4 mmol) and di-*tert*-butyl azodicarboxylate (5.85 g, 25.4 mmol) in anhydrous THF (60 mL) were reacted according to the general procedure for 16 h. Purification by column chromatography (SiO_2, 6:1 petrol/ ethyl acetate) provided **1d** (4.63 g, 99%) as a white solid: m. p. 54–58 °C; υ_{max} (neat)/cm^{-1} 3318, 2931, 1712; δ_H (500

MHz, $CDCl_3$) 6.34 (1H, br s, NH), 6.01–5.87 (1H, m, C*H*CH_3), 4.31 (2H, br s, NCH_2CBr), 1.77 (3H, d, *J* = 6.5 Hz, CHC*H*$_3$), 1.46 (18H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 154.9 (COO), 154.7 (COO), 126.9 (*C*HCH_3, rotamer), 127.6 (*C*HCH_3, rotamer), 123.6 (NCH_2*C*Br), 81.5 (*C*$(CH_3)_3$), 81.3 (*C*$(CH_3)_3$), 58.5 (N*C*H_2CBr, rotamer), 57.4 (N*C*H_2CBr, rotamer), 28.2 (2 x C(*C*$H_3)_3$), 16.7 (CH*C*H_3); MS (ESI^+) *m/z* 387 ($M(^{79}Br)Na^+$), 389 ($M(^{81}Br)Na^+$); HRMS (ESI/TOF-Q) *m/z* $[M + Na]^+$ calcd for $C_{14}H_{25}{}^{79}BrN_2O_4Na$ 387.0890; found 387.0889.

Diethyl 1-(2-bromo-3-methylbut-2-enyl)hydrazine-1,2-dicarboxylate **(1e)**

2-Bromo-3-methylbut-2-en-1-ol (1.00 g, 6.06 mmol), triphenylphosphine (3.17 g, 12.1 mmol) and diethyl azodicarboxylate (1.96 mL, 12.1 mmol) in anhydrous THF (100 mL) were reacted according to the general procedure for 24 h. Purification by column chromatography provided **1e** (1.42 g, 73%) as a colourless oil: υ_{max} (film)/cm^{-1} 3300, 2986, 1704; δ_H (400 MHz, $CDCl_3$) 6.68–6.22 (1H, br m, NH), 4.68–4.42 (2H, m, NCH_2CBr), 4.26–4.16 (4H, m, 2 x CO_2C*H*$_2CH_3$), 1.92 (3H, s, CBr=C(C*H*$_3$)(CH_3)), 1.84 (3H, br s, CBr=C(CH_3)(C*H*$_3$)), 1.27 (6H, t, *J* = 7.1 Hz, 2 x CO_2CH_2C*H*$_3$); δ_C (100 MHz, $CDCl_3$) 156.0 (COO), 155.4 (COO), 137.0 (*C*Br=C$(CH_3)_2$, rotamer), 136.6 (*C*Br=C$(CH_3)_2$, rotamer), 115.4 (CBr=*C*$(CH_3)_2$), 62.5 (CO_2*C*H_2CH_3), 61.9 (CO_2*C*H_2CH_3), 53.8 (N*C*H_2CBr, rotamer), 53.3 (N*C*H_2CBr, rotamer), 25.5 (CBr=C(C*H*$_3$)(CH_3)), 20.4 (CBr=C(CH_3)(C*H*$_3$)), 14.4 (2 x CO_2CH_2*C*H_3); MS (ESI^+) *m/z* 345 ($M(^{79}Br)Na^+$), 347 ($M(^{81}Br)Na^+$); HRMS (ESI/TOF-Q) *m/z* $[M + Na]^+$ calcd for $C_{11}H_{19}{}^{79}BrN_2O_4Na$ 345.0420; found 345.0425.

2-Benzyl 1-(tert-butyl) 1-(2-bromoallyl)hydrazine-1,2-dicarboxylate **(1g)**

To a solution of sodium hydroxide (318 mg, 7.96 mmol) in H_2O (40 mL) and CH_2Cl_2 (40 mL) at 0 °C was added *tert*-butyl 1-(2-bromoallyl)hydrazine-1-carboxylate[22] (2.00 g, 7.96 mmol) followed by the dropwise addition of benzyl chloroformate (1.14 mL, 7.99 mmol). The reaction was allowed to warm to room temperature over 16 h. The solution was diluted with H_2O (40 mL) and the organic layer extracted

with CH_2Cl_2 (3 x 50 mL), washed with 20% citric acid solution (60 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 4:1 petrol/ ethyl acetate) provided **1g** (2.65 g, 86%) as a colourless oil: υ_{max} (film/cm^{-1}) 3297, 2934, 1715, 1632, 1499; δ_H (500 MHz, $CDCl_3$) 7.39–7.31 (5H, m, Ar H), 6.67 (1H, m, NH), 6.38 5.79 (1H, m, C*H*H=CBr), 5.58 (1H, s, CH*H*=CBr), 5.17 (2H, s, CH_2Ar), 4.45–4.16 (2H, m, NCH_2CBr), 1.49 (5H, br s, $C(CH_3)_3$, rotamer), 1.39 (4H, br s, $C(CH_3)_3$, rotamer); δ_C (125 MHz, $CDCl_3$) 155.9 (COO), 154.6 (COO), 135.6 (C, Ar), 128.6 (CH, Ar), 128.5 (CH, Ar), 128.4 (CH, Ar), 128.3 (CH_2=*C*Br), 120.0 (*C*H_2=CBr, rotamer), 119.5 (*C*H_2=CBr, rotamer), 82.7 (*C*$(CH_3)_3$, rotamer), 82.1 (*C*$(CH_3)_3$, rotamer), 67.8 (CH_2Ar), 58.3 (NCH_2, rotamer), 56.9 (NCH_2, rotamer), 28.2 (C(*C*$H_3)_3$, rotamer), 28.0 (C(*C*$H_3)_3$, rotamer); MS (ESI^+) *m/z* 407 (M(^{79}Br)Na^+), 409 (M(^{81}Br)Na^+); HRMS (ESI/TOF-Q) *m/z* $[M + Na]^+$ calcd for $C_{16}H_{21}{}^{79}BrN_2O_4Na$ 407.0577; found 407.0571.

Synthesis of 3-alkylidene-1,2-diazetidines 2b, 2d, 2e and 2g: General Procedure.

To a solution of hydrazine **1** (1.0 molar equiv) in anhydrous THF was added copper (I) iodide (CuI) (0.2 molar equiv), cesium carbonate (Cs_2CO_3) (2 molar equiv) and N,N′-Dimethylethylenediamine (DMEDA) (0.4 molar equiv), and the mixture was heated under reflux until full consumption of the starting material. The reaction was cooled to room temperature and filtered through Celite® with ethyl acetate. The solution was concentrated, passed through a column of silica, eluting with ethyl acetate, dried over $MgSO_4$, filtered, and concentrated in vacuo. Further purification by column chromatography provided the products as detailed below.

Di-iso-propyl 3-methylene-1,2-diazetidine-1,2-dicarboxylate **(2b)**

1b (821 mg, 2.55 mmol), CuI (97 mg, 0.51 mmol), Cs_2CO_3 (1.66 g, 5.10 mmol) and DMEDA (108 μL, 1.02 mmol) in anhydrous THF (20 mL) were reacted according to the general procedure for 16 h. Purification by column chromatography (SiO_2, 4:1 petrol/ ethyl acetate) provided **2b** (567 mg, 92%) as

a colourless oil: υ_{max} (film)/cm^{-1} 2983, 1717; δ_H (400 MHz, $CDCl_3$) 5.10–4.94 (3H, m, C=C*H*H, 2 x C*H*$(CH_3)_2$), 4.66–4.63 (2H, m, NCH_2), 4.42–4.38 (1H, m, C=CH*H*), 1.33 (6H, d, *J* = 6.2 Hz, CH(C*H*$_3)_2$), 1.30 (6H, d, *J* = 6.2 Hz, CH(C*H*$_3)_2$); δ_C (100 MHz, $CDCl_3$) 160.1 (COO), 154.9 (COO), 142.4 (*C*=CH_2), 90.1 (C=*C*H_2), 71.03 (*C*H$(CH_3)_2$), 70.97 (*C*H$(CH_3)_2$), 57.5 (NCH_2), 21.9 (2 x CH_3), 21.8 (2 x CH_3); MS (ESI$^+$) *m/z* 265 (MNa$^+$); HRMS (ESI/TOF-Q) *m/z* [M + Na]$^+$ calcd for $C_{11}H_{18}N_2O_4Na$ 265.1159; found 265.1156.

***Di-tert-butyl (Z)-3-(ethylidene)-1,2-diazetidine-1,2-dicarboxylate* (2d)**

(*Z*)-**1d** (2.00 g, 5.48 mmol), CuI (209 mg, 1.10 mmol), Cs_2CO_3 (3.58 g, 11.0 mmol) and DMEDA (240 μL, 2.20 mmol) in anhydrous THF (34 mL) were reacted according to the general procedure for 5 d. Purification by column chromatography (SiO_2, 10:1 petrol/ ethyl acetate) provided **2d** (990 mg, 64%) as a white solid: m. p. 80–83 °C; υ_{max} (neat)/cm^{-1} 2981, 2937, 1740; δ_H (500 MHz, $CDCl_3$) 4.70 (1H, q, *J* = 7.2 Hz, C*H*CH_3), 4.58 (2H, s, NCH_2), 1.80 (3H, d, *J* = 7.2 Hz, CHC*H*$_3$), 1.53 (9H, s, C(C*H*$_3)_3$), 1.50 (9H, s, C(C*H*$_3)_3$); δ_C (125 MHz, $CDCl_3$) 159.5 (COO), 155.6 (COO), 135.6 (*C*CH_2), 103.5 (*C*HCH_3), 82.8 (*C*$(CH_3)_3$), 82.3 (*C*$(CH_3)_3$), 58.0 (CH_2), 28.14 (C(*C*H$_3)_3$), 28.07 (C(*C*H$_3)_3$), 12.8 (CH*C*H$_3$); MS (ESI$^+$) *m/z* 307 (MNa$^+$); HRMS (ESI/TOF-Q) *m/z* [M + Na]$^+$ calcd for $C_{14}H_{24}N_2O_4Na$ 307.1628; found 307.1630.

***Diethyl 3-(propan-2-ylidene)-1,2-diazetidine-1,2-dicarboxylate* (2e)**

1e (870 mg, 2.69 mmol), CuI (118 mg, 0.62 mmol), Cs_2CO_3 (2.03 g, 6.23 mmol) and DMEDA (132 μL, 1.24 mmol) in anhydrous THF (20 mL) were reacted according to the general procedure for 16 h. Purification by column chromatography (SiO_2, 4:1 petrol/ ethyl acetate) provided **2e** (610 mg, 94%) as a colourless oil: υ_{max} (film)/cm^{-1} 2985, 1710; δ_H (400 MHz, $CDCl_3$) 4.68 (2H, br s, NCH_2), 4.23 (2H, q, *J* = 7.1 Hz, CO_2C*H*$_2CH_3$), 4.22 (2H, q, *J* = 7.1 Hz, CO_2C*H*$_2CH_3$), 1.77 (3H, m, C=C(C*H*$_3$)(CH$_3$)), 1.48 (3H, br s, C=C(CH$_3$)(C*H*$_3$)), 1.29 (3H, t, *J* = 7.1 Hz, CO_2CH_2C*H*$_3$), 1.27 (3H, t, *J* = 7.1 Hz,

$CO_2CH_2CH_3$); δ_C (100 MHz, $CDCl_3$) 160.5 (COO), 157.8 (COO), 129.3 (*C*=C$(CH_3)_2$ or C=*C*$(CH_3)_2$), 113.5 (*C*=C$(CH_3)_2$ or C=*C*$(CH_3)_2$), 62.90 ($CO_2CH_2CH_3$), 62.86 ($CO_2CH_2CH_3$), 58.4 (NCH_2), 18.6 (C=C(*C*H_3)(CH_3)), 18.4 (C=C(CH_3)(*C*H_3)), 14.4 ($CO_2CH_2CH_3$), 14.3 ($CO_2CH_2CH_3$); MS (ESI^+) *m/z* 265 (MNa^+); HRMS (ESI/TOF-Q) *m/z* $[M + Na]^+$ calcd for $C_{11}H_{18}N_2O_4Na$ 265.1159; found: 265.1155.

***2-Benzyl 1-(tert-butyl) 3-methylene-1,2-diazetidine-1,2-dicarboxylate* (2g)**

1g (108 mg, 0.28 mmol), CuI (11 mg, 58 μmol), Cs_2CO_3 (182 mg, 0.56 mmol) and DMEDA (12 μL, 0.11 mmol) in anhydrous THF (8 mL) were reacted according to the general procedure for 3 d. Purification by column chromatography (SiO_2, 6:1 petrol/ ethyl acetate) provided **2g** (53 mg, 62%) as a colourless oil: υ_{max} (film)/cm^{-1} 2933, 1736, 1718, 1498; δ_H (500 MHz, $CDCl_3$) 7.41–7.32 (5H, m, Ar H), 5.26 (2H, s, CH_2Ar), 4.99–4.94 (1H, m, C=C*H*H), 4.62 (1H, d, *J* = 2.2 Hz, NC*H*H), 4.61 (1H, d, *J* = 2.2 Hz, NCH*H*), 4.43–4.40 (1H, m, C=CH*H*), 1.45 (9H, s, C$(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 159.4 (*C*O_2C$(CH_3)_3$), 155.2 (*C*O_2CH_2Ar), 142.3 (*C*=CH_2), 135.3 (C, Ar), 128.6 (CH, Ar), 128.4 (CH, Ar), 128.1 (CH, Ar), 90.6 (C=*C*H_2), 83.0 (*C*$(CH_3)_3$), 68.3 (CH_2Ar), 57.5 (NCH_2), 27.9 (C(*C*$H_3)_3$); MS (ESI^+) *m/z* 327 (MNa^+); HRMS (ESI/TOF-Q) *m/z* $[M + Na]^+$ calcd for $C_{16}H_{20}N_2O_4Na$ 327.1315; found 327.1315.

Synthesis of 1,1-difluoro-4,5-diazaspiro[2.3]hexanes 3a-e: General procedure.

To a sealed tube was added 3-methylene-1,2-diazetidine (1.0 molar equiv) and sodium iodide (0.2 molar equiv) in anhydrous THF. Trimethyl(trifluoromethyl)silane ($TMSCF_3$) (2.5 molar equiv) was added, and the sealed tube heated at 65 °C until full consumption of the starting material. The reaction was cooled to room temperature and concentrated in vacuo. The residue was diluted with diethyl ether (20 mL) and washed with H_2O (15 mL), saturated aqueous Na_2SO_3 solution (15 mL), saturated aqueous sodium bicarbonate solution (15 mL) and H_2O (15 mL). The organic extract was dried over $MgSO_4$, filtered,

and concentrated in vacuo. Purification by column chromatography provided the products as detailed below.

Di-tert-butyl 1,1-difluoro-4,5-diazaspiro[2.3]hexane-4,5-dicarboxylate **(3a)**

1,2-Diazetidine **2c** (90 mg, 0.33 mmol), sodium iodide (10 mg, 67 μmol) and $TMSCF_3$ (123 μL, 0.83 mmol) in anhydrous THF (3 mL) were reacted according to the general procedure for 5 h. Purification by flash column chromatography (SiO_2, 5:1 petrol/ ethyl acetate) provided **3a** (103 mg, 97%) as a white solid: m. p. 96–99 °C; υ_{max} (neat)/cm^{-1} 2974, 2933, 1737; δ_H (500 MHz, $CDCl_3$) 4.34 (1H, d, *J* = 8.4 Hz, NC*H*H), 4.22 (1H, dd, *J* = 8.4, 4.6 Hz, NCH*H*), 2.65 (1H, ddd, *J* = 15.0, 10.1, 4.9 Hz, C*H*HCF_2), 1.51 (9H, s, $C(CH_3)_3$), 1.49 (9H, s, $C(CH_3)_3$), 1.43 (1H, ddd, *J* = 15.3, 10.1, 5.2 Hz, CH*H*CF_2); δ_C (125 MHz, $CDCl_3$) 159.5 (COO), 156.8 (COO), 106.9 (dd, J_{CF} = 293.4, 289.9 Hz, CF_2), 83.2 (*C*$(CH_3)_3$), 82.8 (*C*$(CH_3)_3$), 52.5 (NCH_2), 50.0 (dd, J_{CF} = 15.8, 9.8 Hz, *C*CH_2), 28.1 (2 x C(*C*$H_3)_3$), 16.7 (t, J_{CF} = 10.6 Hz, C*C*H_2); δ_F (376 MHz, $CDCl_3$) –136.7 (d, J_{FF} = 170 Hz), –142.8 (d, J_{FF} = 169 Hz); MS (ESI^+) *m/z* 343 (MNa^+); HRMS (ESI/TOF-Q) *m/z* $[M + Na]^+$ calcd for $C_{14}H_{22}F_2N_2O_4Na$ 343.1440; found 343.1435.

(2S*,3S*)-Di-tert-butyl 1,1-difluoro-2-methyl-4,5-diazaspiro[2.3]hexane-4,5-dicarboxylate **(3b)**

1,2-Diazetidine **2d** (85 mg, 0.30 mmol), sodium iodide (9 mg, 60 μmol) and $TMSCF_3$ (111 μL, 0.75 mmol) in anhydrous THF (3 mL) were reacted according to the general procedure for 6 h. Purification by flash column chromatography (SiO_2, 9:1 petrol/ ethyl acetate) provided (2*S**,3*S**)-**3b** (80 mg, 80%) as a colourless oil: υ_{max} (film)/cm^{-1} 2980, 2936, 1714; δ_H (400 MHz, $CDCl_3$) 4.31 (1H, d, *J* = 8.2 Hz, NC*H*H), 3.97 (1H, dd, *J* = 8.1, 2.7 Hz, NCH*H*), 1.60–1.51 (1H, m, C*H*CH_3), 1.47 (9H, s, $C(CH_3)_3$), 1.46 (9H, s, $C(CH_3)_3$), 1.32 (3H, d, *J* = 6.7 Hz, CHC*H*$_3$); δ_C (125 MHz, $CDCl_3$) 159.3 (COO), 156.2 (COO), 109.8 (dd, J_{CF} = 304.5, 296.1 Hz, CF_2), 83.0 (*C*$(CH_3)_3$), 82.5 (*C*$(CH_3)_3$), 53.1 (dd, J_{CF} = 14.1, 8.1 Hz, *C*CH_2), 52.6 (d, J_{CF} = 6.0 Hz, C*C*H_2), 28.1 (C(*C*$H_3)_3$), 27.7 (C(*C*$H_3)_3$), 24.8 (t, J_{CF} = 9.9 Hz, *C*HCH_3), 5.3 (d, J_{CF} = 4.3 Hz, CH*C*H_3); δ_F (376 MHz, $CDCl_3$) –125.8 (d, J_{FF} = 167 Hz), –147.9 (d, J_{FF} = 167 Hz);

MS (ESI$^+$) *m/z* 357 (MNa$^+$); HRMS (ESI/TOF-Q) *m/z* [M + Na]$^+$ calcd for $C_{15}H_{24}F_2N_2O_4Na$ 357.1596; found 357.1598.

Di-tert-butyl 1,1-difluoro-(2,2-dimethyl)-4,5-diazaspiro[2.3]hexane-4,5-dicarboxylate **(3c)**

1,2-Diazetidine **2f** (90 mg, 0.30 mmol), sodium iodide (9 mg, 60 μmol) and $TMSCF_3$ (111 μL, 0.75 mmol) in anhydrous THF (3 mL) were reacted according to the general procedure for 5 h. Purification by flash column chromatography (SiO_2, 9:1 petrol/ ethyl acetate) provided **3c** (100 mg, 96%) as a white solid: m. p. 85–87 °C; υ_{max} (neat)/cm^{-1} 2980, 2935, 1727; δ_H (500 MHz, $CDCl_3$) 4.18 (1H, dd, *J* = 8.3, 1.9 Hz, NC*H*H), 3.95 (1H, dd, *J* = 8.3, 5.4 Hz, NCH*H*), 1.50 (9H, s, C(CH_3)$_3$), 1.48 (9H, s, C(CH_3)$_3$), 1.38 (3H, s, C(C*H*$_3$)(CH$_3$)), 1.08 (3H, s, C(CH$_3$)(C*H*$_3$)); δ_C (125 MHz, $CDCl_3$) 159.3 (COO), 156.5 (COO), 111.2 (dd, J_{CF} = 309.6, 299.8 Hz, CF_2), 83.0 (*C*(CH$_3$)$_3$), 82.5 (*C*(CH$_3$)$_3$), 55.6 (dd, J_{CF} = 13.1, 8.9 Hz, *C*CH$_2$), 49.4 (d, J_{CF} = 5.9 Hz, C*C*H$_2$), 28.1 (C(*C*H$_3$)$_3$), 27.8 (C(*C*H$_3$)$_3$), 26.2 (t, J_{CF} = 9.9 Hz, *C*(CH$_3$)$_2$), 14.7 (d, J_{CF} = 7.6 Hz, C(*C*H$_3$)(CH$_3$)), 13.2 (d, J_{CF} = 5.8 Hz, C(CH$_3$)(*C*H$_3$)); δ_F (376 MHz, $CDCl_3$) –136.4 (d, J_{FF} = 164 Hz), –144.9 (d, J_{FF} = 164 Hz); MS (ESI$^+$) *m/z* 371 (MNa$^+$); HRMS (ESI/TOF-Q) *m/z* [M + Na]$^+$ calcd for $C_{16}H_{26}F_2N_2O_4Na$ 371.1753; found 371.1751.

4-Benzyl 5-(tert-butyl) 1,1-difluoro-4,5-diazaspiro[2.3]hexane-4,5-dicarboxylate **(3d)**

1,2-Diazetidine **2g** (371 mg, 1.22 mmol), sodium iodide (36 mg, 0.24 mmol), $TMSCF_3$ (451 μL, 3.05 mmol) in anhydrous THF (15 mL) were reacted according to the general procedure for 4 h. Purification by flash column chromatography (SiO_2, 5:1 petrol/ ethyl acetate) provided **3d** (347 mg, 80%) as a colourless oil: υ_{max} (film)/cm^{-1} 2931, 1714, 1496; δ_H (500 MHz, $CDCl_3$) 7.41–7.29 (5H, m, Ar H), 5.27 (1H, d, *J* = 12.3 Hz, C*H*HAr), 5.15 (1H, d, *J* = 12.3 Hz, CH*H*Ar), 4.37 (1H, d, *J* = 8.5 Hz, NC*H*H), 4.27 (1H, dd, *J* = 8.5, 4.6 Hz, NCH*H*), 2.69 (1H, ddd, *J* = 15.1, 10.3, 4.8 Hz, C*H*HCF$_2$), 1.45 (9H, s, C(CH$_3$)$_3$), 1.44-1.39 (1H, m, CH*H*CF$_2$); δ_C (125 MHz, $CDCl_3$) 159.3 (COO), 158.2 (COO), 135.1 (C, Ar), 128.6 (CH, Ar), 128.4 (CH, Ar), 128.1 (CH, Ar), 106.6 (dd, J_{CF} = 292.3, 290.3 Hz, CF_2), 83.2

($C(CH_3)_3$), 68.3 (CH_2Ar), 52.8 (NCH_2), 50.8 (dd, J_{CF} = 16.0, 10.0 Hz, CCF_2), 28.0 ($C(CH_3)_3$), 16.6 (t, J_{CF} = 11.0 Hz, CH_2CF_2); δ_F (376 MHz, $CDCl_3$) –137.4 (d, J_{FF} = 170 Hz), –142.8 (d, J_{FF} = 170 Hz); MS (ESI^+) *m/z* 377 (MNa^+); HRMS (ESI/TOF-Q) *m/z* $[M + Na]^+$ calcd for $C_{17}H_{20}F_2N_2O_4Na$ 377.1283; found 377.1287.

Diethyl 1,1-difluoro-4,5-diazaspiro[2.3]hexane-4,5-dicarboxylate **(3e)**

1,2-Diazetidine **2a** (56 mg, 0.26 mmol), sodium iodide (8 mg, 53 μmol), $TMSCF_3$ (96 μL, 0.65 mmol) in anhydrous THF (3 mL) were reacted according to the general procedure for 6 h. Purification by flash column chromatography (SiO_2, 4:1 petrol/ ethyl acetate) provided **3e** (32 mg, 47%) as a colourless oil: υ_{max} (film)/cm^{-1} 2984, 2937, 1713; δ_H (500 MHz, $CDCl_3$) 4.42 (1H, d, *J* = 8.4 Hz, NC*H*H), 4.35 (1H, dd, *J* = 8.5, 4.6 Hz, NCH*H*), 4.32–4.17 (4H, m, 2 x CH_2CH_3), 2.72 (1H, ddd, *J* = 15.2, 10.6, 5.2 Hz, C*H*HCF_2), 1.48 (1H, ddd, *J* = 15.5, 10.6, 5.8 Hz, CH*H*CF_2), 1.33–1.27 (6H, m, 2 x CH_2CH_3); δ_C (125 MHz, $CDCl_3$) 160.6 (COO), 158.2 (COO), 106.6 (dd, J_{CF} = 292.2, 290.3 Hz, CF_2), 63.2 (CH_2CH_3), 63.1 (CH_2CH_3), 53.0 (NCH_2), 51.0 (dd, J_{CF} = 15.9, 10.1 Hz, CCH_2), 16.6 (t, J_{CF} = 11.0 Hz, CH_2CF_2), 14.33 (CH_2CH_3), 14.28 (CH_2CH_3); δ_F (376 MHz, $CDCl_3$) –137.5 (d, J_{FF} = 170 Hz), –143.1 (d, J_{FF} = 170 Hz); MS (ESI^+) *m/z* 287 (MNa^+); HRMS (ESI/TOF-Q) *m/z* $[M + Na]^+$ calcd for $C_{10}H_{14}F_2N_2O_4Na$ 287.0814; found 287.0821.

Benzyl 1,1-difluoro-4,5-diazaspiro[2.3]hexane-4-carboxylate **(4)**

To a solution of **3d** (82 mg, 0.23 mmol) in anhydrous CH_2Cl_2 (5 mL) under an atmosphere of nitrogen was added trifluoroacetic acid (176 μL, 2.30 mmol) dropwise. The reaction was stirred at room temperature for 5 h and then concentrated. The residue was diluted with CH_2Cl_2 (10 mL), and washed with saturated aqueous sodium bicarbonate solution (10 mL) and H_2O (10 mL). The aqueous layer was washed with CH_2Cl_2 (10 mL), the organic extracts combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to provide **4** (53 mg, 91%) as a yellow oil: υ_{max} (film)/cm^{-1} 3259, 3030, 2962,

2899, 1709, 1492; δ_H (400 MHz, $CDCl_3$) 7.38–7.29 (5H, m, Ar H), 5.60 (1H, br s, NH), 5.22 (1H, d, *J* = 12.2 Hz, C*H*HAr), 5.11 (1H, d *J* = 12.2 Hz, CH*H*Ar), 4.07 (1H, br m, CC*H*H), 3.87 (1H, br m, CCH*H*), 2.67 (1H, br m, C*H*HCF$_2$), 1.38 (1H, ddd, *J* = 15.5, 10.1, 5.2 Hz, CH*H*CF$_2$); δ_C (125 MHz, $CDCl_3$) 157.9 (COO), 135.5 (C, Ar), 128.6 (CH, Ar), 128.4 (CH, Ar), 128.3 (CH, Ar), 107.4 (t, J_{CF} = 291.9 Hz, CF_2), 67.7 (CH_2Ar), 53.5 (dd, J_{CF} = 16.2, 9.8 Hz, *C*CH_2), 46.2 (C*C*H_2), 17.2 (t, J_{CF} = 9.4 Hz, *C*H_2CF_2); δ_F (376 MHz, $CDCl_3$) –137.7 (d, J_{FF} = 169 Hz), –142.7 (d, J_{FF} = 169 Hz); MS (ESI$^+$) *m/z* 255 (MH^+), 277 (MNa^+); HRMS (ESI/TOF-Q) *m/z* [M + Na]$^+$ calcd for $C_{12}H_{12}F_2N_2O_2Na$ 277.0759; found 277.0763.

Synthesis of 1,1-dichloro-4,5-diazaspiro[2.3]hexanes 5a-e: General procedure.

To a solution of 3-methylene-1,2-diazetidine (1.0 molar equiv) in chloroform was added benzyltriethylammonium (TEBAC) (10 mol %) and aqueous NaOH solution (50 wt %) dropwise. The reaction was stirred vigorously at room temperature until full consumption of the starting material. The solution was neutralized by addition of saturated aqueous NH_4Cl solution (20 mL). The mixture was extracted with EtOAc (3 x 30 mL) and the combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography provided the products as detailed below.

***Di-tert-butyl 1,1-dichloro-4,5-diazaspiro[2.3]hexane-4,5-dicarboxylate* (5a) and *di-tert-butyl 1,1-dichloro-5-oxo-4,6-diazaspiro[2.4]heptane-4,6-dicarboxylate* (6)**

1,2-Diazetidine **2c** (103 mg, 0.38 mmol), TEBAC (9 mg, 39 μmol), aqueous NaOH solution (5 mL, 50 wt %) in chloroform (10 mL) were reacted according to the general procedure for 3 h. Purification by column chromatography (SiO_2, 9:1 petrol/ ethyl acetate) provided less polar **5a** (64 mg, 48%) as a white solid: m. p. 122–125 °C; υ_{max} (neat)/cm^{-1} 3088, 2980, 2934, 1725; δ_H (500 MHz, $CDCl_3$) 4.41 (1H, d, *J* = 8.9 Hz, NC*H*H), 4.29 (1H, d, *J* = 8.9 Hz, NCH*H*), 2.79 (1H, d, *J* = 9.5 Hz, C*H*HCCl$_2$), 1.57–1.51 (10H, m, CH*H*CCl$_2$, C(CH$_3$)$_3$), 1.49 (9H, s, C(CH$_3$)$_3$); δ_C (125 MHz, $CDCl_3$) 159.4 (COO), 156.9

(COO), 83.2 (*C*$(CH_3)_3$), 82.7 (*C*$(CH_3)_3$), 57.4 (CCl_2 or *C*CH_2), 56.0 (CCl_2 or *C*CH_2), 54.1 (NCH_2), 28.1 (2 x C(*C*$H_3)_3$), 25.6 (CH_2Cl_2); MS (ESI^+) *m/z* 375 ($M(^{35}Cl)Na^+$), 377 ($M(^{37}Cl)Na^+$); HRMS (ESI/TOF-Q) *m/z* $[M + Na]^+$ calcd for $C_{14}H_{22}{}^{35}Cl_2N_2O_4Na$ 375.0849; found 375.0849. Further elution provided more polar **6** (60 mg, 41%) as a white solid: m. p. 124–127 °C; υ_{max} (neat)/cm^{-1} 3110, 2981, 2929, 1782, 1729, 1366, 1267, 1138, 769; δ_H (500 MHz, $CDCl_3$) 4.10 (1H, d, *J* = 11.4 Hz, NC*H*H), 3.81 (1H, d, *J* = 11.3 Hz, NCH*H*), 3.36 (1H, d, *J* = 9.7 Hz, C*H*HCCl_2), 1.67 (1H, d, *J* = 9.7 Hz, CH*H*CCl_2), 1.55 (9H, s, C$(CH_3)_3$), 1.50 (9H, s, C$(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 149.7 (C=O), 149.6 (COO), 148.6 (COO), 84.4 (*C*$(CH_3)_3$), 84.1 (*C*$(CH_3)_3$), 61.6 (CCl_2 or *C*CH_2), 46.9 (CCl_2 or *C*CH_2), 46.0 (NCH_2), 28.1 (*C*H_2CCl_2), 28.0 (C(*C*$H_3)_3$), 27.9 (C(*C*$H_3)_3$); MS (ESI^+) *m/z* 403 ($M(^{35}Cl)Na^+$), 405 ($M(^{37}Cl)Na^+$); HRMS (ESI/TOF-Q) *m/z* $[M + Na]^+$ calcd for $C_{15}H_{22}{}^{35}Cl_2N_2O_5Na$ 403.0798; found 403.0800.

(2S*,3S*)-Di-tert-butyl 1,1-dichloro-2-methyl-4,5-diazaspiro[2.3]hexane-4,5-dicarboxylate **(5b)**

1,2-Diazetidine **2d** (85 mg, 0.30 mmol), TEBAC (7 mg, 31 μmol) and aqueous NaOH solution (5 mL, 50 wt %) in chloroform (10 mL) were reacted according to the general procedure for 15 min. Purification by flash column chromatography (SiO_2, 9:1 petrol/ ethyl acetate) provided (2*S**,3*S**)-**5b** (46 mg, 42%) as a colourless oil: υ_{max} (film)/cm^{-1} 2979, 2934, 1713; δ_H (500 MHz, $CDCl_3$) 4.32 (1H, d, *J* = 8.6 Hz, NC*H*H), 4.13 (1H, d, *J* = 8.6 Hz, NCH*H*), 1.63 (1H, q, *J* = 6.8 Hz, C*H*CH_3), 1.53 (3H, d, *J* = 6.7 Hz, CHC*H*$_3$), 1.49 (9H, s, C$(CH_3)_3$), 1.46 (9H, s, C$(CH_3)_3$); δ_C (125 MHz, $CDCl_3$) 159.4 (COO), 155.6 (COO), 82.9 (*C*$(CH_3)_3$), 82.5 (*C*$(CH_3)_3$), 63.2 (CCl_2 or *C*CH_2), 59.0 (CCl_2 or *C*CH_2), 55.0 (CH_2), 34.9 (*C*HCH_3), 28.1 (C(*C*$H_3)_3$), 27.9 (C(*C*$H_3)_3$), 10.7 (CH*C*H_3); MS (ESI^+) *m/z* 389 ($M(^{35}Cl)Na^+$), 391 ($M(^{37}Cl)Na^+$); HRMS (ESI/TOF-Q) *m/z* $[M + Na]^+$ calcd for $C_{15}H_{24}{}^{35}Cl_2N_2O_4Na$ 389.1005; found 389.1004.

Di-tert-butyl-1,1-dichloro-(2,2-dimethyl)-4,5-diazaspiro[2.3]hexane-4,5-dicarboxylate **(5c)**

1,2-Diazetidine **2f** (90 mg, 0.30 mmol), TEBAC (7 mg, 31 μmol) and aqueous NaOH solution (5 mL, 50 wt %) in chloroform (10 mL) were reacted according to the general procedure for 75 min. Purification by flash column chromatography (SiO_2, 9:1 petrol/ ethyl acetate) provided **5c** (65 mg, 57%) as a white solid: m. p. 103–106 °C; υ_{max} (neat)/cm^{-1} 2978, 2932, 1715; δ_H (400 MHz, $CDCl_3$) 4.12 (2H, q, *J* = 8.4 Hz, NCH_2), 1.59 (3H, s, $C(CH_3)(CH_3)$), 1.50 (9H, $C(CH_3)_3$), 1.48 (9H, s, $C(CH_3)_3$), 1.16 (3H, s, $C(CH_3)(CH_3)$); δ_C (125 MHz, $CDCl_3$) 159.4 (COO), 155.4 (COO), 82.8 ($C(CH_3)_3$), 82.5 ($C(CH_3)_3$), 68.7 (CCl_2 or CCH_2), 62.0 (CCl_2 or CCH_2), 52.3 (NCH_2), 32.4 ($C(CH_3)_2$), 28.1 ($C(CH_3)_3$), 27.9 ($C(CH_3)_3$), 20.9 ($C(CH_3)(CH_3)$), 19.3 ($C(CH_3)(CH_3)$); MS (ESI^+) *m/z* 403 ($M(^{35}Cl)Na^+$), 405 ($M(^{37}Cl)Na^+$); HRMS (ESI/TOF-Q) *m/z* $[M + Na]^+$ calcd for $C_{16}H_{26}{}^{35}Cl_2N_2O_4Na$ 403.1162; found 403.1161.

Diethyl 1,1-dichloro-4,5-diazaspiro[2.3]hexane-4,5-dicarboxylate **(5d)**

1,2-Diazetidine **2a** (75 mg, 0.35 mmol), TEBAC (8 mg, 35 μmol) and aqueous NaOH solution (5 mL, 50 wt %) in chloroform (10 mL) were reacted according to the general procedure for 6 h. Purification by flash column chromatography (SiO_2, 4:1 petrol/ ethyl acetate) provided **5d** (67 mg, 64%) as a colourless oil: υ_{max} (film)/cm^{-1} 3087, 2985, 2924, 1724, 1467; δ_H (500 MHz, $CDCl_3$) 4.47 (1H, d, *J* = 9.0 Hz, NC*H*H), 4.38 (1H, d, *J* = 9.0 Hz, NCH*H*), 4.33–4.15 (4H, m, 2 x CH_2CH_3), 2.84 (1H, d, *J* = 9.7 Hz, C*H*HCCl_2), 1.57 (1H, d, *J* = 9.8 Hz, CH*H*CCl_2), 1.33–1.25 (6H, m, 2 x CH_2CH_3); δ_C (125 MHz, $CDCl_3$) 160.5 (COO), 158.3 (COO), 63.2 (CH_2CH_3), 63.1 (CH_2CH_3), 57.2 (CCl_2 or CCH_2), 56.5 (CCl_2 or CCH_2), 54.5 (NCH_2), 25.6 (CH_2CCl_2), 14.4 (CH_2CH_3), 14.3 (CH_2CH_3); MS (ESI^+) *m/z* 319 ($M(^{35}Cl)Na^+$), 321 ($M(^{37}Cl)Na^+$); HRMS (ESI/TOF-Q) *m/z* $[M + Na]^+$ calcd for $C_{10}H_{14}{}^{35}Cl_2N_2O_4Na$ 319.0223; found 319.0221.

Di-tert-butyl 1,1-difluoro-5-oxo-4,6-diazaspiro[2.4]heptane-4,6-dicarboxylate **(7)**

To **3a** (28 mg, 87 μmol) and TEBAC (2 mg, 9 μmol) in chloroform (3 mL) was added aqueous sodium hydroxide (1.5 mL, 50 wt%) dropwise. The reaction was stirred vigorously at room temperature for 6 h, then neutralized with saturated aqueous NH_4Cl solution (10 mL). The mixture was extracted with EtOAc (3 x 10 mL) and the combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography (SiO_2, 4:1 petrol/ ethyl acetate) provided **7** (18 mg, 59%) as a white solid: m. p. 118–121 °C; υ_{max} (film)/cm^{-1} 3111, 2973, 2934, 1789, 1718; δ_H (400 MHz, $CDCl_3$) 3.87 (1H, d, *J* = 10.7 Hz, NC*H*H), 3.69 (1H, dd, *J* = 10.8, 6.4 Hz, NCH*H*), 3.21 (1H, ddd, *J* = 13.4, 9.9, 5.5 Hz, C*H*HCF$_2$), 1.54 (9H, s, C(CH$_3$)$_3$), 1.52 (9H, s, C(CH$_3$)$_3$), 1.48–1.44 (1H, m CH*H*CF$_2$); δ_C (125 MHz, $CDCl_3$) 149.6 (C=O), 149.1 (COO), 148.6 (COO), 108.8 (t, J_{CF} = 294.8 Hz, CF_2), 84.5 (*C*(CH$_3$)$_3$), 84.0 (*C*(CH$_3$)$_3$), 43.7 (d, J_{CF} = 6.5 Hz, NCH_2), 41.9 (dd, J_{CF} = 10.9, 9.3 Hz, *C*CF$_2$), 28.0 (C(*C*H$_3$)$_3$), 27.9 (C(*C*H$_3$)$_3$), 18.5 (t, J_{CF} = 10.3 Hz, *C*H$_2$CF$_2$); δ_F (376 MHz, $CDCl_3$) –125.8 (d, J_{FF} = 167 Hz), –147.9 (d, J_{FF} = 167 Hz); MS (ESI$^+$) *m/z* 371 (MNa$^+$); HRMS (ESI/TOF-Q) *m/z* [M + Na]$^+$ calcd for $C_{15}H_{22}F_2N_2O_5Na$ 371.1389; found 371.1389.

Synthesis of diazaspiro[3.3]heptanes 9a-f: General procedure

To a solution of 3-methylene-1,2-diazetidine (1.0 molar equiv) in CH_2Cl_2 (3 mL) at 0 °C was added tetracyanoethylene (TCNE) (1.0 molar equiv). The solution was allowed to warm to room temperature until full consumption of the starting material and concentrated in vacuo. Purification provided the products as detailed below.

Di-tert-butyl-5,5,6,6-tetracyano-1,2-diazaspiro[3.3]heptane-1,2-dicarboxylate **(9a)**

1,2-Diazetidine **2c** (50 mg, 0.19 mmol), TCNE (24 mg, 0.19 mmol) and CH_2Cl_2 (3 mL) were reacted according to the general procedure for 16 h. Recrystallization from ethyl acetate provided **9a** (52 mg, 71%) as a white crystalline solid: m.p. 145–146 °C; υ_{max} (neat)/cm^{-1} 2981, 1705; δ_H (400 MHz, acetone-*d*$_6$) 4.88 (1H, d, *J* = 10.4 Hz, NC*H*H), 4.62 (1H, d, *J* = 10.4 Hz, NCH*H*), 4.51 (1H, d, *J* = 15.2 Hz,

C*H*HC(CN)$_2$), 3.99 (1H, d, *J* = 15.2 Hz, CH*H*C(CN)$_2$), 1.55 (9H, s, C(CH$_3$)$_3$), 1.51 (9H, s, C(CH$_3$)$_3$); δ_C (100 MHz, acetone-d_6) 159.9 (COO), 154.7 (COO), 112.6 (CN), 112.1 (CN), 110.2 (CN), 109.3 (CN), 84.9 (*C*(CH$_3$)$_3$), 83.5 (*C*(CH$_3$)), 70.1 (*C*CH$_2$ or *C*(CN)$_2$), 59.6 (NCH$_2$), 50.7 (*C*CH$_2$ or *C*(CN)$_2$), 42.2 (*C*H$_2$C(CN)$_2$), 32.2 (CH$_2$*C*(CN)$_2$), 28.2 (C(*C*H$_3$)$_3$), 28.1 (C(*C*H$_3$)$_3$); MS (ESI$^+$) *m/z* 421 (MNa$^+$); HRMS (ESI/TOF-Q) *m/z* [M + Na]$^+$ calcd for $C_{19}H_{22}N_6O_4Na$ 421.1595; found 421.1593.

***Di-iso-propyl 5,5,6,6-tetracyano-1,2-diazaspiro[3.3]heptane-1,2-dicarboxylate* (9b)**

1,2-Diazetidine **2b** (50 mg, 0.21 mmol), TCNE (26 mg, 0.21 mmol) and CH_2Cl_2 (3 mL) were reacted according to the general procedure for 16 h. Recrystallization from ethyl acetate provided **9b** (59 mg, 77%) as a white crystalline solid: m.p. 172–173 °C; υ_{max} (neat)/cm^{-1} 2986, 2365, 1704; δ_H (400 MHz, CD$_3$CN) 5.08 (1H, sep, *J* = 6.3 Hz, CO$_2$C*H*(CH$_3$)$_2$), 4.95 (1H, sep, *J* = 6.3 Hz, CO$_2$C*H*(CH$_3$)$_2$), 4.53 (1H, d, *J* = 10.4 Hz, NC*H*H), 4.49 (1H, d, *J* = 10.4 Hz, NCH*H*), 4.18 (1H, d, *J* = 15.8 Hz, C*H*HC(CN)$_2$), 3.65 (1H, d, *J* = 15.8 Hz, CH*H*C(CN)$_2$), 1.33 (6H, dd, *J* = 8.0, 6.3 Hz, CO$_2$CH(C*H*$_3$)$_2$), 1.27 (6H, t, *J* = 6.4 Hz, CO$_2$CH(C*H*$_3$)$_2$); δ_C (100 MHz, CD$_3$CN) 159.3 (2 x COO), 111.2 (CN), 110.8 (CN), 108.5 (CN), 107.8 (CN), 72.1 (1C, *C*H(CH$_3$)$_2$), 71.0 (1C, *C*H(CH$_3$)$_2$), 68.4 (*C*CH$_2$ or *C*(CN)$_2$), 57.9 (NCH$_2$), 49.8 (*C*CH$_2$ or *C*(CN)$_2$), 40.5 (*C*H$_2$C(CN)$_2$), 31.7 (CH$_2$*C*(CN)$_2$), 20.8 (CH(*C*H$_3$)(CH$_3$)), 20.74 (CH(CH$_3$)(*C*H$_3$)), 20.69 (CH(*C*H$_3$)(CH$_3$)), 20.62 (CH(CH$_3$)(*C*H$_3$)); MS (ESI$^+$) *m/z* 393 (MNa$^+$); HRMS (ESI/TOF-Q) *m/z* [M + Na]$^+$ calcd for $C_{17}H_{18}N_6O_4Na$ 393.1282; found 393.1284.

***Diethyl 5,5,6,6-tetracyano-1,2-diazaspiro[3.3]heptane-1,2-dicarboxylate* (9c)**

1,2-Diazetidine **2a** (50 mg, 0.23 mmol), TCNE (30 mg, 0.23 mmol) and CH_2Cl_2 (3 mL) were reacted according to the general procedure for 16 h. Recrystallization from ethyl acetate provided **9c** (67 mg, 84%) as a white crystalline solid: m.p. 184–185 °C; υ_{max} (neat)/cm^{-1} 2985, 1718; δ_H (400 MHz, CD$_3$CN), 4.55 (1H, d, *J* = 10.2 Hz, NC*H*H), 4.50 (1H, d, *J* = 10.3 Hz, NCH*H*), 4.38–4.12 (5H, m, C*H*HC(CN)$_2$), 2 x CO$_2$C*H*$_2$CH$_3$), 3.67 (1H, d, *J* = 16.0 Hz, CH*H*C(CN)$_2$), 1.31 (3H, t, *J* = 7.1 Hz,

$CO_2CH_2CH_3$), 1.27 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$); δ_C (100 MHz, CD_3CN) 159.1 (COO), 155.2 (COO), 111.2 (CN), 110.7 (CN), 108.4 (CN), 107.8 (CN), 68.3 (CCH_2 or $C(CN)_2$), 63.3 ($CO_2CH_2CH_3$), 62.7 ($CO_2CH_2CH_3$), 57.7 (NCH_2), 49.3 (CCH_2 or $C(CN)_2$), 40.6 ($CH_2C(CN)_2$), 31.4 ($CH_2C(CN)_2$), 13.27 ($CO_2CH_2CH_3$), 13.25 ($CO_2CH_2CH_3$); MS (ESI^+) *m/z* 365 (MNa^+); HRMS (ESI/TOF-Q) *m/z* [M + Na]$^+$ calcd for $C_{15}H_{14}N_6O_4Na$ 365.0969; found 365.0967.

***1-Benzyl 2-(tert-butyl) 5,5,6,6-tetracyano-1,2-diazaspiro[3.3]heptane-1,2-dicarboxylate* (9d)**

1,2-Diazetidine **2g** (50 mg, 0.17 mmol), TCNE (21 mg, 0.17 mmol) and CH_2Cl_2 (3 mL) were reacted according to the general procedure. Additional TCNE (10 mg, 0.08 mmol) was added after 20 h at 0 °C, and the reaction warmed to room temperature and stirred for 6 h until completion, then concentrated in vacuo. Purification by flash column chromatography (SiO_2, 2:1 petrol/ ethyl acetate) provided **9d** (71 mg, 99%) as a white solid: m.p. 149–151 °C; υ_{max} (neat)/cm^{-1} 2988, 1714, 1502; δ_H (500 MHz, acetone-d_6) 7.48 (2H, d, *J* = 7.3 Hz, Ar H), 7.43–7.31 (3H, m, Ar H), 5.38 (1H, d, *J* = 12.5 Hz, C*H*HAr), 5.25 (1H, d, *J* = 12.5 Hz, CH*H*Ar), 4.91 (1H, d, *J* = 10.4 Hz, NC*H*H), 4.68 (1H, d, *J* = 10.4 Hz, NCH*H*), 4.52 (1H, d, *J* = 15.4 Hz, C*H*HC(CN)$_2$), 4.03 (1H, d, *J* = 15.4 Hz, CH*H*C(CN)$_2$), 1.44 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, acetone-d_6) 158.8 (COO), 155.5 (COO), 135.5 (C, Ar), 128.4 (CH, Ar), 128.3 (CH, Ar), 128.1 (CH, Ar), 111.8 (CN), 111.2 (CN), 109.3 (CN), 108.3 (CN), 82.8 ($C(CH_3)_3$), 69.7 (CCH_2 or $C(CN)_2$), 68.2 (CH_2Ar), 58.8 (NCH_2), 50.2 (CCH_2 or $C(CN)_2$), 40.9 ($CH_2C(CN)_2$), 31.7 ($CH_2C(CN)_2$), 27.2 ($C(CH_3)_3$); MS (ESI^+) *m/z* 455 (MNa^+); Anal. calcd for $C_{22}H_{20}N_6O_4$: C, 61.10; H, 4.66; N, 19.43%. Found: C, 61.17; H, 4.71; N, 19.05%.

***(3R*,7S*)-Di-tert-butyl 5,5,6,6-tetracyano-7-methyl-1,2-diazaspiro[3.3]heptane-1,2-dicarboxylate* (9e)**

1,2-Diazetidine **2d** (51 mg, 0.18 mmol), TCNE (23 mg, 0.18 mmol) and CH_2Cl_2 (3 mL) were reacted according to the general procedure for 16 h to give a 4:1 mixture of diastereomers. Purification by flash column chromatography (SiO_2, 5:1 petrol / ethyl acetate) provided the major diastereomer (3*R**,7*S**)-**9e**

(54 mg, 73%) as a white solid: m.p. 65–68 °C; υ_{max} (neat)/cm^{-1} 2981, 2937, 1717; δ_H (500 MHz, acetone-*d*$_6$) 4.94 (1H, d, *J* = 10.9 Hz, NC*H*H), 4.80 (1H, q, *J* = 7.0 Hz, C*H*CH$_3$), 4.43 (1H, d, *J* = 10.8 Hz, NCH*H*), 1.70 (3H, d, *J* = 7.1 Hz, CHC*H*$_3$), 1.55 (9H, s, C(CH$_3$)$_3$), 1.51 (9H, s, C(CH$_3$)$_3$); δ_C (125 MHz, acetone-*d*$_6$) 158.6 (COO), 153.8 (COO), 110.5 (CN), 109.1 (CN), 109.0 (CN), 108.6 (CN), 84.4 (*C*(CH$_3$)$_3$), 82.9 (*C*(CH$_3$)$_3$), 73.2 (*C*CH$_2$ or *C*(CN)$_2$), 53.4 (NCH$_2$), 48.4 (*C*CH$_2$ or *C*(CN)$_2$), 45.5 (*C*HCH$_3$), 37.3 (CH*C*(CN)$_2$), 27.21 (C(*C*H$_3$)$_3$), 27.19 (C(*C*H$_3$)$_3$), 11.4 (CH*C*H$_3$); MS (ESI$^+$) *m/z* 435 (MNa$^+$); Anal. calcd for $C_{20}H_{24}N_6O_4$: C, 58.24; H, 5.87; N, 20.38%. Found: C, 58.21; H, 5.91; N, 20.24%.

Diethyl 5,5,6,6-tetracyano-7,7-dimethyl-1,2-diazaspiro[3.3]heptane-1,2-dicarboxylate **(9f)**

1,2-Diazetidine **2e** (50 mg, 0.21 mmol), TCNE (26 mg, 0.21 mmol) and CH_2Cl_2 (3 mL) were reacted according to the general procedure for 16 h. Recrystallization from ethyl acetate provided **9f** (30 mg, 39%) as a white crystalline solid: m.p. 137–138 °C; υ_{max} (neat)/cm^{-1} 2989, 2333, 1727; δ_H (400 MHz, CD$_3$CN) 4.46 (1H, d, *J* = 10.5 Hz, NC*H*H), 4.44–4.35 (2H, m, NCH*H*, CO$_2$C*H*HCH$_3$), 4.28-4.17 (3H, m, CO$_2$CH*H*CH$_3$, CO$_2$C*H*$_2$CH$_3$), 1.68 (3H, s, C(C*H*$_3$)(CH$_3$)), 1.60 (3H, s, C(CH$_3$)(C*H*$_3$)), 1.32 (3H, t, *J* = 7.1 Hz, CO$_2$CH$_2$C*H*$_3$), 1.27 (3H, t, *J* = 7.1 Hz, CO$_2$CH$_2$C*H*$_3$); δ_C (100 MHz, CD$_3$CN) 159.2 (COO), 153.8 (COO), 109.8 (CN), 109.5 (CN), 109.1 (CN), 107.3 (CN), 76.3 (C), 63.0 (CO$_2$*C*H$_2$CH$_3$), 62.9 (CO$_2$*C*H$_2$CH$_3$), 53.9 (NCH$_2$), 53.1 (C), 45.2 (C), 24.2 (C(*C*H$_3$)(CH$_3$)), 20.9 (C(CH$_3$)(*C*H$_3$)), 13.22 (CO$_2$CH$_2$C*H*$_3$), 13.18 (CO$_2$CH$_2$C*H*$_3$), one quaternary carbon not observed; MS (ESI$^+$) *m/z* 393 (MNa$^+$); HRMS (ESI/TOF-Q) *m/z* [M + H]$^+$ calcd for $C_{17}H_{19}N_6O_4$ 371.1462; found 371.1465.

ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H, ^{13}C and ^{19}F NMR spectra for new compounds, and X-ray crystal structure (CIF) files for **3a**, **5a**, **6** and **9b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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NOTES

The authors declare no competing financial interest.

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